IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant: Philip C. Comp

Serial No.: 08/323,060 Art Unit: 1644

Filed: October 14, 1994 Examiner: Ronald B. Schwadron

For: *"BLOCKAGE OF PROTEIN C ACTIVATION REDUCES MICROVASCULAR SURGICAL BLOOD LOSS"*

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUBSTITUTE APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 1-6, 11-13 and 19 in the Office Action mailed December 13, 2002, in the above-identified patent application. Submitted with this Substitute Appeal Brief is an Amendment in response to the Notice of Non-Compliance mailed November 3, 2003. A Notice of Appeal was mailed on April 17, 2003. A Petition for an Extension of Time for One Month was enclosed with the Brief mailed on July 17, 2003. The Commissioner was authorized when the Appeal Brief was initially mailed on July 17, 2003 to charge the fee for filing of an Appeal Brief and Petition for an Extension of Time for One Month, one month, up to and including July 17, 2003, by a small entity, to Deposit Account No. 50-1868. It is believed that no fee is required with this submission. However, should a fee be

required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-1868.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is Oklahoma Medical Research Foundation, Oklahoma City, OK, the assignee.

(2) RELATED APPEALS AND INTERFERENCES

This case was previously on Appeal before the Board of Patent Appeals and Interferences (Appeal No. 1999-2254). In the Decision, the Board affirmed the rejection of claims 14-16 under 35 U.S.C. § 112, first and second paragraphs. The Board reversed all other rejections as they applied to claims 1-9, 11-13 and 19-21.

(3) STATUS OF CLAIMS ON APPEAL

Claims 1-9, 11-13, and 19-21 are pending. Claims 10 and 14-18 have been canceled. Claims 7-9, 20 and 21 are allowable. Claims 1-6, 11-13, and 19 are on appeal. The text of each claim as pending is set forth in an Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

An Amendment after final rejection was submitted on August 13, 2003. In the Office Action mailed November 3, 2003, the Examiner indicated that this amendment would be entered if submitted in the appropriate format. An Amendment in the appropriate format accompanies this Appeal Brief. An Appendix sets forth the claims as pending.

(5) SUMMARY OF THE INVENTION

The claims are drawn to a method for inhibiting microvascular bleeding at a site in a patient by administering to the patient a compound in an effective amount to prevent anticoagulation by greater than 90% of activated protein C in human plasma, wherein the compound is an inhibitor of protein C, antithrombin III, heparin cofactor II, thrombomodulin or tissue factor pathway inhibitor (see page 14, lines 21-27; claim 1). The inhibitor may be administered systemically or topically (see page 14, lines 12-17). One may additionally administer a coagulant topically to the site of the bleeding (see page 14, lines 13-15, claim 5). The coagulant may be thrombin or tissue thromboplastin (see page 13, lines 6-16 and lines 27-30, claim 6). The inhibitor may be an antibody to protein C (see page 18, lines 18-31). The inhibitor may be administered systemically and a coagulant administered topically at the site of bleeding (page 14, lines 13-15). The topically administered coagulant may be thrombin in a dosage of between approximately 1000 and 10,000 units or tissue factor in a dosage of between approximately 0.1 and 10 mg (see page 16, lines 25-27, claim 9). The inhibitor may be administered to a burn patient, a patient with tissue or skin grafts, or a patient with cerebral contusions (see page 14, lines 1-3; and lines 8-11). The inhibitor may be a monoclonal antibody that is immunoreactive with protein C and blocks protein C activation (see page 18, lines 13-21) such as HPC-4 (see page 12, lines 9-29; page 14, lines 21-27; and page 18, lines 13-21).

(6) ISSUES ON APPEAL

The issue presented on appeal is whether claims 1-6, 11-13, and 19 meet the written description requirement as required by 35 U.S.C. § 112, first paragraph.

(7) GROUPING OF CLAIMS

Claims 1-6, 11-3, and 19 stand or fall together with respect to the single basis on which the claims have been rejected as not in compliance with the written description requirement under 35 U.S.C. 112, for not being limited to an antibody.

(8) ARGUMENTS

(a) The Claimed Invention

The claims define a method for reducing blood loss from microvascular bleeding due to wounds caused by surgery or trauma, in particular bleeding from skin graft donor sites, burns, bleeding liver surfaces, and inflamed visceral surfaces. These types of injuries are particularly difficult to treat. Burns, for example, may cover a large surface area and ooze for days due to the massive inflammation and loss of epidermal cover. Liver is highly vascularized and if cut to remove a tumor or during transplant, may bleed for extended periods of time. Unlike a more typical cut or wound, microvascular bleeding is extremely difficult to control. The prior art method of treatment typically consisted of topical administration of thrombin, which sometimes worked, but often had little efficacy.

Appellant, Dr. Comp, is a medical doctor and researcher in the field of blood clotting disorders and the components involved in this process. In the late 1980's, he and Dr. Charles Esmon discovered that an inhibitor of a natural anticoagulant, protein C, could be used to kill

tumors. They used a monoclonal antibody immunoreactive with protein C, but not the "activated" form of protein C, referred to as HPC-4, in their studies in a variety of animal species having a number of different solid tumors to demonstrate efficacy. This discovery formed the basis of a patent application which issued with claims to methods and compositions for inhibition of tumors in 1992 as U.S. Patent No. 5,147,638 to Charles Esmon and Philip Comp. An earlier filed application issued with claims to the HPC-4 antibody in 1993 as U.S. Patent No. 5,202,253 to Charles and Naomi Esmon.

The method for treating tumors was enhanced by the use of a cytokine, such as tumor necrosis factor, and was thought to kill the tumors by causing massive microvascular clotting within the tumors but not in normal tissue. It was not known why the systemic or local administration of the inhibitor, alone or in combination with a cytokine, did not cause clotting to occur in tissues other than the tumors, however, extensive autopsies showed the results were consistent in all animal models tested, including dogs, cats, pigs, and baboon.

Dr. Comp subsequently determined that systemic administration of an inhibitor of a natural anticoagulant, such as protein C, could also be used to inhibit microvascular bleeding in normal patients. This is typical of injuries such as in burn and skin graft patients, where large areas "ooze" fluids, causing extensive fluid loss, and pain due to adhesion to bandages, as well as serving as entry sites for infection. It also occurs in brain trauma patients, where it is extremely difficult to treat without the risk of a clot forming and causing a stroke.

Dr. Comp conducted his experiments in pigs, removing areas of skin grafts (0.015 inches in thickness, application page 17). He treated the injured tissue with either (1) systemic HPC4;

(2) systemic HPC4 with topical thrombin; (3) systemic HPC4 with topical thromboplastin; (4) saline control; (5) topical thrombin (prior art treatment); topical thromboplastinc (application page 18). The analysis of the various treatments showed that systemic HPC4 was generally equivalent to the results obtained with topical throbmin or tissue thromboplastin, demonstrating the efficacy of systemic treatment of microvascular bleeding using an inhibitor of a natural anticoagulant. The analysis also demonstrated that the combination of systemic inhibitor with topical coagulant achieved a 33 to 44% decrease in blood loss ($p < 0.05$) as compared with either systemic administration of inhibitor alone or topical thrombin alone (page 20, Figures 2 and 3).

The claimed methods define the use of an inhibitor of one or more natural anticoagulants: protein C, thrombomodulin, antithrombin II, heparin cofactor II or tissue factor pathway inhibitor, in an amount effective to prevent anticoagulation.

As is clear from the attached diagram of the clotting cascade, clotting components added in concert - not alone. This diagram shows protein C as "PC"; activated protein C as "APC", and thrombomodulin as "TM", and how these interact, so that inhibition at any point will inhibit anticoagulation - and allow clotting to occur. Although not shown in this diagram, antithrombin III, heparin cofactor II, and tissue factor pathway inhibitor play the same type of roles in anticoagulation, so that inhibition of any of these molecules will also block the protein C anticoagulation pathway.

At the time of filing the present application, components of the coagulation pathway were known. Antibodies to protein C and inhibitors of the other components of the coagulation

process were also known. The board previously acknowledged this when they found appellant's composition claims unpatentable over the prior art.

However, the issue on appeal is not enablement or prior art but whether or not the disclosure of known materials in the application, along with actual reduction to practice of one embodiment of the claimed method, meets the written description requirement under 35 U.S.C. 112.

(b) Rejections Under 35 U.S.C. § 112

i. The Legal Standard for Written Description

As the Court of Appeals for the Federal Circuit recently stated in Amgen v. Hoechst, et al. 314 F.3d 1313, 65 USPQ2d 1385 (Fed. Cir. 2003),

"the purpose of the written description requirement is to prevent an Appellant from later asserting that he invented that which he did not; the Appellant for a patent is therefore required to "recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1561, 19 USPQ2d 111, 1115 (Fed. Cir. 1991). Satisfaction of this requirement is measured by the understanding of the ordinarily skilled artisan. Lockwood v. Am. Airlines, Inc. , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997) ("The description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). "Compliance with the written description requirement is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" Enzo Biochem v. Gen-Probe, Inc., 296 F.3d 1316, 1324, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002) (citation omitted)."

The Court of Appeal for the Federal Circuit's decision in Eli Lilly v. Univ. of Calif. Board of Regents In Regents of University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997), *cert denied*, 523 U.S. 1089 (1998) is not applicable in this case. The claims in this case are not drawn to claims to a protein or a gene encoding a protein, but to a method of use of known materials. In Enzo Biochem, the Federal Circuit held that that the written description requirement can be met by a functional description of *claimed materials*, if coupled with a known or disclosed correlation between function and structure. Enzo Biochem, Inc., v. Gen-Probe, Inc., 296 F.3d 1316, 63 U.S.P.Q.2d 1609 (Fed. Cir.2002) ("*Enzo II*"). Enzo is also not applicable in this case, again since appellant is claiming a method of using known materials, not the materials themselves.

In Amgen, the Federal Circuit upheld the lower court's claim construction and its decision that the claims comply with the written description and enablement requirements of 35 U.S.C. § 112, stating

"Both Eli Lilly and Enzo Biochem are inapposite to this case because the claim terms at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend." Reiterating, the Court stated that the standard was merely that "the patent specification must contain "a written description of the invention, and of the manner and process of making and using it...[such] as to enable any person of ordinary skill in the art to which it pertains ... to make and use the same ... " "The specification does not need to teach what is already known in the art. The specification is enabled if one of ordinary skill in the art only engages in routine experimentation to make the invention."

ii. Rejection of Claims 1-6, 11-13 and 19 under 35 U.S.C. § 112, first paragraph

The specification clearly discloses the proteins to be inhibited (anticoagulants) and types of inhibitors such as antibodies; there has been no argument in this respect. The specification also states that other types of inhibitors can be used (bottom of page 12 to top of page 13).

The basis for the rejection is the Examiner's assertion that the only inhibitor of an anticoagulant disclosed in the specification is an antibody which binds the anticoagulant recited in the claims. This is patently untrue. The specification clearly defines other targets than protein C. Antibodies to the other proteins/anticoagulants were also known and available at the time of filing the present application. Evidence in the form of the references submitted with the Amendment mailed on September 23, 2002, clearly shows that the activity of the anticoagulants recited in the claims could be inhibited by proteins and/or DNA oligonucleotides that were known as of the filing date of this application (see, for example, *J. Histochem. Cytochem.*, 1994 (10):1365-1376 **[anti-thrombin III antibody]**; *Hybridoma*, 1991(5)633-640 **[anti-thrombin III antibody]**; *J. Heart Lung Transpant.* 1992(2 pt. 1):342-347 **[anti-thrombin III antibody]**; *J. Histochem. Cytochem.*, 1994(10):1365-1376 **[anti-thrombin III antibody]**; *J. Chromatography*, 1991(2):493-500 **[heparin cofactor II antiserum]**; *Thromb. Haemost* 1992(5):507-509 **[thrombomodulin antibodies]**; *Kidney Int.*, 1992(5):1170-1174 **[thrombomodulin antibodies]**; and *Thromb. Haemost.*, 1992(3):310-314 **[tissue factor pathway inhibitor antibody]**). Other inhibitors of clotting protein were known and could therefore be used in the claimed method (see, for example, *Gene*, 1993, 137(1):25-31 **[inhibition of thrombin *via* single**

stranded DNA oligonucleotides] in combination with *Seminars in Hematology*, Vol. 29 (3):159-169, 1992).

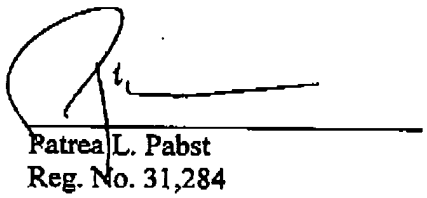
The examiner has apparently refused to consider these references on the ground that they were not recited in the specification. However, that is not the test. Appellant has demonstrated that the materials were known to these skilled in the art as of the effective filing date. Appellant has pointed to where in the specification one is told to use inhibitors of these anticoagulants, not just antibodies, not just to protein C. Therefore, one skilled in the art would not only be enabled, but the written description in the application as filed would be sufficient to describe to one skilled in the art what the invention is, in full compliance with 35 U.S.C. 112.

(9) SUMMARY AND CONCLUSION

Since the compounds required by the claimed method were known as of the time of filing, and are recited in the application as filed, even if not actually reduced to practice, in a way that one of ordinary skill in the art would be able to make and use the claimed method, all claims are in compliance with the written description requirement under 35 U.S.C. 112.

For the foregoing reasons, Appellant submits that all claims 1-9, 11-13, and 19-21 are patentable.

Respectfully submitted,



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Appendix: Claims as Pending

1. A method for inhibiting microvascular bleeding at a site in a patient exhibiting microvascular bleeding comprising administering to the patient a compound in a pharmaceutically acceptable carrier in an effective amount to prevent anticoagulation by greater than 90% of activated protein C in human plasma, wherein the compound is an inhibitor of an anticoagulant selected from the group consisting of protein C, antithrombin III, heparin cofactor II, thrombomodulin and tissue factor pathway inhibitor.

2. The method of claim 1 wherein the anticoagulant is protein C.

3. The method of claim 1 wherein the inhibitor is administered systemically.

4. The method of claim 1 wherein the inhibitor is administered topically.

5. The method of claim 1 further comprising topically administering at the site of the bleeding a coagulant.

6. The method of claim 5 wherein the coagulant is selected from the group consisting of thrombin and tissue thromboplastin.

7. A method for inhibiting microvascular bleeding at a site in a patient exhibiting microvascular bleeding comprising administering to the patient an antibody to protein C in a pharmaceutically acceptable carrier in an effective amount to prevent anticoagulation by greater than 90% of activated protein C in human plasma.

8. The method of claim 7 further comprising the step of topically administering a coagulant at the site of bleeding.

9. The method of claim 8 wherein the topically administered coagulant is selected from the group consisting of thrombin in a dosage of between approximately 1000 and 10,000 units and tissue factor in a dosage of between approximately 0.1 and 10 mg.

11. The method of claim 1 wherein the inhibitor is administered to a burn patient.

12. The method of claim 1 wherein the inhibitor is administered to a patient with tissue or skin grafts.

13. The method of claim 1 wherein the inhibitor is administered to a patient with cerebral contusions.

19. The method of claim 4 further comprising the step of topically administering a coagulant at the site of bleeding.

20. A method for inhibiting microvascular bleeding at a site in a patient exhibiting microvascular bleeding comprising systemically administering to the patient a monoclonal antibody to protein C which blocks protein C activation in a pharmaceutically acceptable carrier in an effective amount to prevent anticoagulation by greater than 90% of activated protein C in human plasma.

21. The method of claim 20 wherein the antibody is HPC-4, deposited with the American Type Culture Collection, Rockville, MD and assigned ATCC No. 9892.

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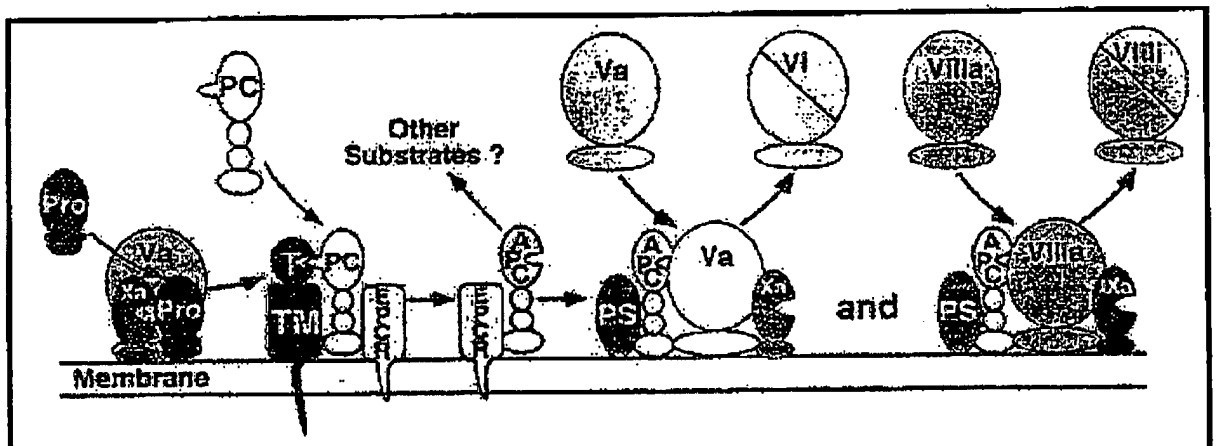

Figure 1. Model of the function of the protein C anticoagulant pathway. Thrombin (T) is generated from prothrombin (Pro) by the factor Va–factor Xa complex. T then binds to thrombomodulin (TM) to form the protein C activation complex. Protein C binds to the endothelial cell protein C receptor (EPCR), if present, and this complex is activated by the T/TM complex. Activated protein C (APC) can remain bound to EPCR, but this complex does not appear to be capable of inactivating factor Va, presumably an indication that it is targeted to as-yet unidentified alternative substrates. When APC dissociates from EPCR, it can then bind to protein S (PS). This complex inactivates factor Va or factor VIIIa, thereby shutting down T formation and preventing blood clot extension. (Modified figure reprinted with permission from Stearns-Kurosawa DJ, Kurosawa S, Mollica JS, Ferrell GL, Esmon CT. The endothelial cell protein C receptor augments protein C activation by the thrombin-thrombomodulin complex. *Proc Natl Acad Sci U S A* 1996;93:10212–10216; Esmon CT. The protein C anticoagulant pathway. *Arterioscler Thromb Vasc Biol* 1992;12:135–145.)[3]

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